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Patentanmeldung Nr. Patent application No. Demande de brevet n°

02012566.2

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

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Anmeldung Nr:
Application no.: 02012566.2
Demande no:

Anmeldetag:
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Anmelder/Applicant(s)/Demandeur(s):

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ALLEMAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

Beta-secretase inhibitors

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Beta-secretase inhibitors

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Beta secretase inhibitors

Description

The invention relates to novel beta-secretase inhibitors.

Beta-secretase (memapsin 2) is a membrane-associated aspartic protease that is involved in the production of beta-amyloid peptide. The beta-amyloid peptide is generated through proteolytic cleavage of the membrane-anchored beta-amyloid precursor protein. Beta-amyloid peptide constitutes one major component of senile plaques.

Senile plaques as well as neurofibrillary tangles in the central nervous tissue, however, are observed in connection with Alzheimer's disease. It is a widely accepted theory that these morphological abnormalities cause the typical cognitive malfunction (dementia) associated with Alzheimer's disease.

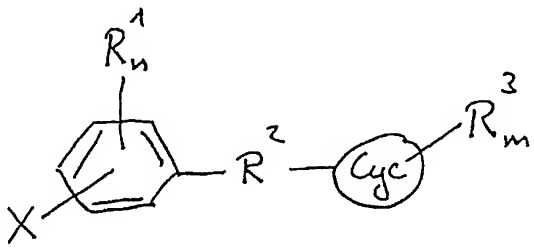
Inhibition of beta-secretase may prevent generation of senile plaques and can therefore stop the progression of Alzheimer's disease (Hong et al., Science 290 (2000) 150-153).

Therefore, much effort has been undertaken to identify beta-secretase inhibitors. Inhibitors identified to date include OM991 as well as OM992, whereby the beta-secretase:OM992 complex also has been crystallized and the structure has been determined up to a resolution of 1.9Å (Ghosh et al., J.Am.Chem.Soc. 122 (2000) 3522-3523; Hong et al., Science 290 (2000) 150-153). Both, OM991 and OM992 are peptidomimetics.

However, since Alzheimer's disease is a wide-spread disease, with about 4 million people suffering therefrom in the U.S. alone, there is still a great need for further effective substances to treat that disease.

Therefore, it was an object of the invention to provide effective beta-secretase inhibitors.

According to the invention this object is achieved by a beta-secretase inhibitor of formula (I)



wherein

X represents a halogen or a moiety which is bioisosteric thereto, in particular, F, Cl, Br or I, preferably Cl,

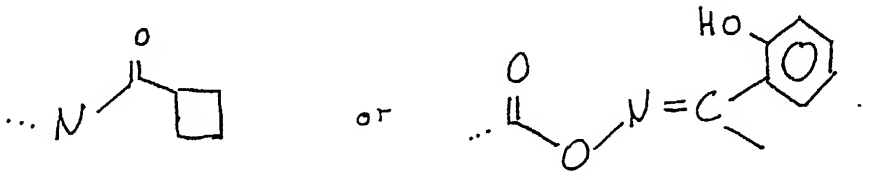
R^1 each independently represents OH or a halogen or a moiety which is bioisosteric thereto, in particular, F, Cl, Br or I, preferably Cl, and n = 0 to 4, preferably n = 0 to 2,

R^2 is a connecting moiety selected from the group consisting of a single bond, a C_1-C_4 alkylene group, a C_2-C_8 alkenylene group, a C_1-C_4 alkylene group containing a least one heteroatom or C_1-C_4 alkenylene group containing at least one heteratom,

Cyc is a cyclic moiety selected from mono- and polycycles being aromatic or non-aromatic and optionally containing one or more heteroatoms selected from O, N and S, and

R^3 each independently is a group being bound to the moiety Cyc and selected from halogen, NO_2, O, N, S or C_1-C_4 alkyl, C_2-C_4 alkenyl, aromatic or non-aromatic cyclic systems which, in turn, can be non-

substituted or substituted with a halogen, a OH, a C_1-C_4 alkyl or a C_1-C_4 alkenyl group, or a group selected from



and

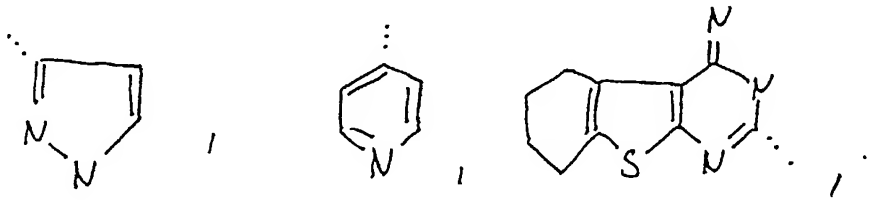
m = 0 to 8, in particular 0 to 4.

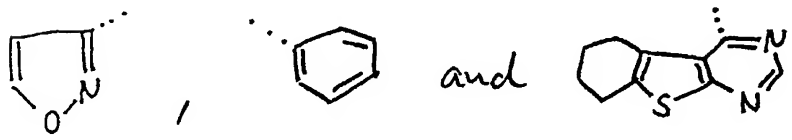
The beta-secretase inhibitors of the invention are characterized by the presence of a halophenyl group, in particular, a chlorophenyl group, whereby a parachlorophenyl group, a diorthochlorophenyl group as well as a dimetachlorophenyl group are preferred. The phenyl group furthermore can be substituted with an OH group, with a dimetachloro-ortho-hydroxy-phenyl group being preferred.

The group X can be in ortho, meta or para position.

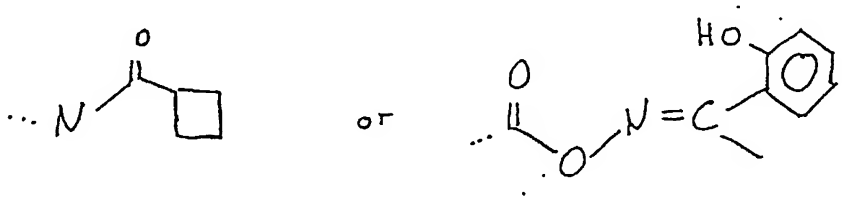
In the beta-secretase inhibitors of the invention a connecting moiety is bound to the chlorophenyl group consisting of a single bond, a C_1-C_4 alkylene group, a C_2-C_8 alkenylene group, a C_1-C_4 alkylene group containing a least one heteroatom or C_1-C_4 alkenylene group containing at least one heteratom, preferably 1 to 3, more preferably 1 to 2 heteroatoms. Preferably, the one or more heteroatoms are selected from N, O and S, more preferably from N and S. Most preferred are connecting moieties R^2 containing two N atoms. The connecting moiety preferably is a single bond, a $-CH_2-S-$, a $-CH=N-N-$ group or a $-C(CH_3)=N-N-$ group.

The connecting moiety R^2 connects the halophenyl residue, in particular, a chlorophenyl residue with a further cyclic moiety. Said second cycle can be a mono- or polycycle, in particular, a polycycle condensed from of two, three or four cycles. The cyclic moiety preferably contains one or more heteroatoms selected from O, N and S. Especially preferred examples of the Cyc group are



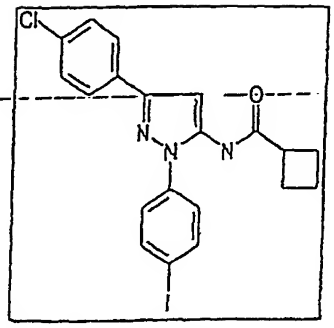


According to the invention the cyclic moiety Cyc again can be substituted with up to eight substituents, preferably up to five substituents. Examples of particularly preferred substituents on the cyclic moiety Cyc are Cl, N, methyl, allyl, paraiodophenyl, NO_2, CF_3 as well as



Most preferably, the beta-secretase inhibitor of the invention is selected from the following compounds:

ID 1



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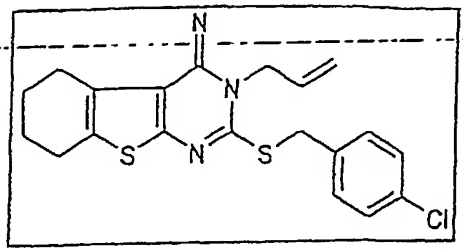

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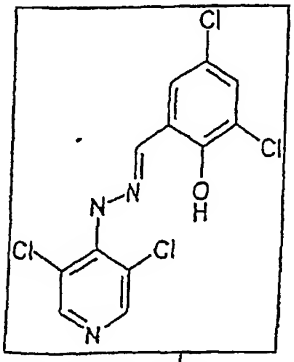

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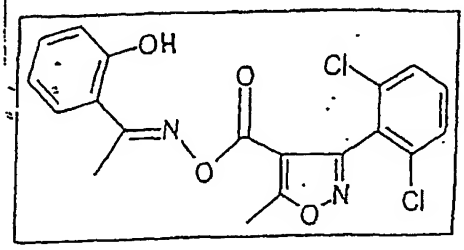
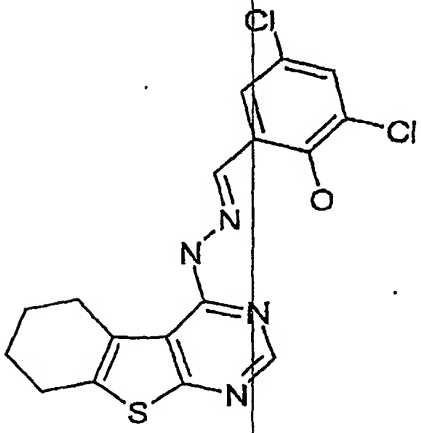
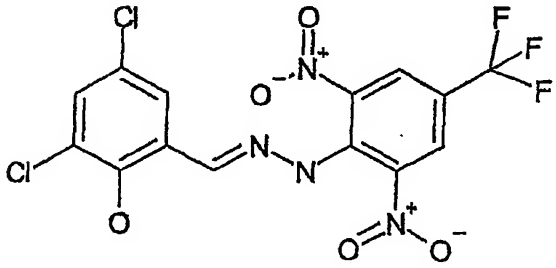


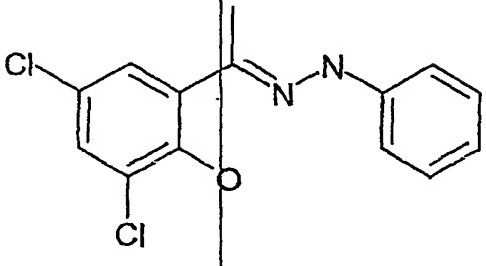
ID 5 (IC_{50}=53,0µM)

ID 6 (IC_{50}=39,3µM)





ID 7 (IC_{50}=14,4µM)



The beta-secretase inhibitors of the invention are potent compounds, by means of which beta-secretase can be inhibited selectively and effectively. They are characterized, in particular, by IC50 values of $\leq$ 200 μM. Further, the compounds of the invention provide new scaffolds for the development of novel drugs based on beta-secretase inhibitors.

The compounds of the invention were identified by applying computerized screening, especially PHACIR screening, for the generation of a focussed library out of a compound data base based on a combined pharmacophore. In this way it is possible to discover beta-secretase inhibitors having new structures, which had not yet been presumed in the art to have such activity.

As combined pharmacophore, for example, a common pharmacophore for aspartyl proteases and a surface-based (surf2lead®) pharmacophore of the crystallized beta-secretase:OM922 complex can be used. For the common pharmacophore of the aspartyl proteases the active center was employed for generation of the pharmacophore. For the surf2lead approach the surface of the active center of the beta-secretase:OM922 complex crystallized with inhibitor was used for generation of the pharmacophore. A query for PHACIR screening was generated from a combination of the two pharmacophores. The compounds of the focussed library identified by virtual screening then can be subjected to an in vitro assay, e.g. a fluorescence BACE assay, in order to thus determine possible inhibitory action of the compounds.

As described above, compounds having beta-secretase inhibitory action are suitable agents for the treatment of Alzheimer's disease. The invention therefore also relates to a pharmaceutical composition comprising a beta-secretase inhibitor as described above, optionally in admixture with one or more pharmaceutically acceptable carriers, diluents and/or excipients.

The pharmaceutical composition can be formulated for administration according to the respective demands. In particular, it can be formulated for topical, oral, transdermal, parenteral, inhalative or intravenous administration.

The amount of inventive inhibitor required for administration in the treatment and/or prophylaxis of Alzheimer's disease depends on the seriousness of the condition as well as on the patient to be treated. Typically, a daily dose is 0.01 mg/kg of body weight to 500 mg/kg of body weight, preferably at least 0.1 mg/kg of body weight to 50 mg/kg of body weight.

Besides the beta-secretase inhibitor the pharmaceutical compositions of the invention can contain one or more other active substances.

The invention further relates to the use of a beta-secretase inhibitor as described above for the manufacture of a drug for the treatment of diseases which are mediated by beta-secretase. The beta-secretase inhibitors are especially suited for the production of a drug for the treatment of Alzheimer's disease. The expression "treatment of a condition" as used herein refers both to the treatment of established symptoms and a prophylactic treatment, by which the occurrence of the disease or particular symptoms can be avoided.

The invention is further illustrated by the following Example.

Example 1

Fluorescence BACE assay

The inhibitory activity of the compounds of the invention was shown in an in vitro assay, namely a fluorescence BACE assay.

The assay was set up in triplicate wells of 96 well black plate. rhBACE was diluted to 1 unit/well in 100 µl (PBS + 0.5% Triton-X 100, pH5). BACE enzyme (obtained from R&D systems (ca.No.931-AS), reference: Vasser et al., 1999, Science 286, 735-741) was incubated with various concentrations of inhibitor compound (10 nM to 500 µM) for 5 min. Reaction was started by adding peptide substrate (obtained from BACHEM (cat. No.M-2470), reference: Ermolieff et al., Biochemistry 39 (2000) 12450-56) with EDANS/Dabcyl labels. After incubation for 2 hours at 37°C the results were read in fluoroplate reader at 355 nm/486 nm.

The following IC50 values were determined for the above-mentioned particularly preferred compounds:

ID1: IC50 = 38 µM; ID2: IC50 = 52 µM; ID3: IC50 = 90 µM; ID4: IC50 = 140-170 µM; ID5: IC50 = 53 µM; ID6: IC50 = 39.3 µM and ID7: IC50 = 14.4 µM.

EPO - Munich
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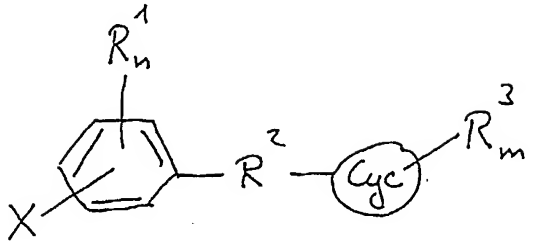
05. Juni 2002

Claims

1. Beta-secretase inhibitor of formula (I)



wherein

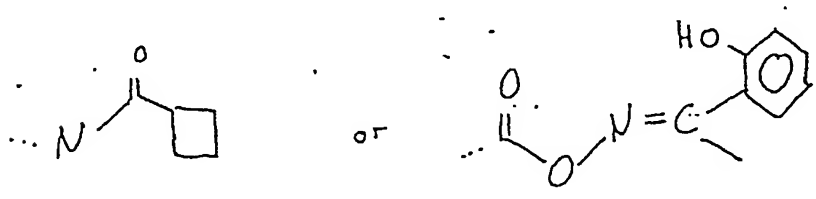
X represents a halogen or a moiety which is bioisosteric thereto,

R^1 each independently represents OH or a halogen or a moiety which is bioisosteric thereto, and n = 0 to 4,

R^2 is a connecting moiety selected from the group consisting of a single bond, a C_1-C_4 alkylene group, a C_2-C_8 alkenylene group, a C_1-C_4 alkylene group containing a least one heteroatom or a C_1-C_4 alkenylene group containing at least one heteratom,

Cyc is a cyclic moiety selected from monocycles and polycycles being aromatic or non-aromatic and optionally containing one or more heteroatoms selected from O, N and S, and

R^3 each independently is a group being bound to the moiety Cyc and selected from halogen, O, N, S, NO_2 or C_1-C_4 alkyl, C_2-C_4 alkenyl, O, N, S, aromatic or non-aromatic cyclic systems which, in turn, can be non-substituted or substituted with halogen, OH, a C_1-C_4 alkyl or a C_1-C_4 alkenyl group, or a group selected from

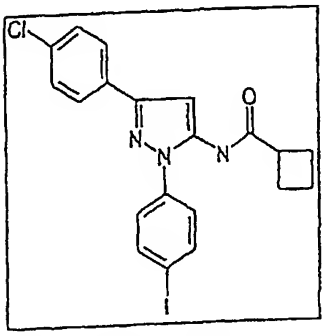


and

m = 0 to 8.

2. Beta-secretase inhibitor according to claim 1 having the formula

ID 1



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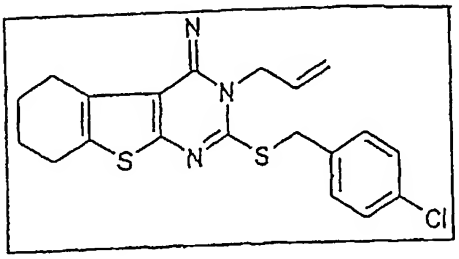

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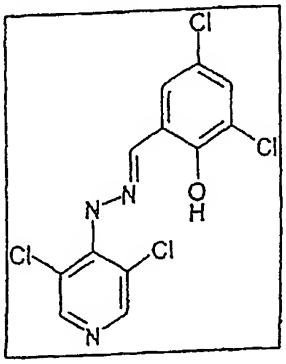

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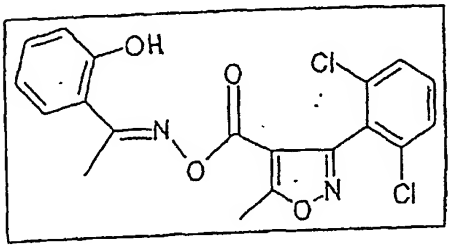
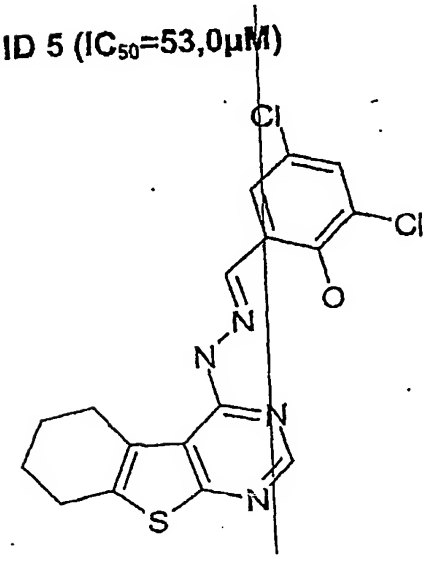


ID 5 (IC_{50}=53,0µM)



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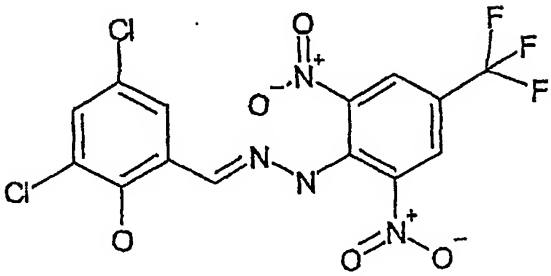
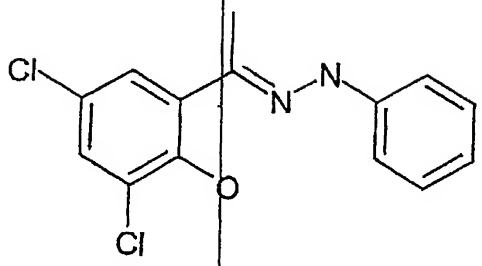


ID 7 (IC_{50}=14,4µM)

or



3. Beta-secretase inhibitor according to claim 1 or 2, having an IC50 ≤ 200 μM.

4. A pharmaceutical composition comprising a beta-secretase inhibitor according to any of claims 1 to 3, optionally in admixture with one or more pharmaceutically acceptable carriers, diluents and/or excipients.

5. The use of a beta-secretase inhibitor according to any of claims 1 to 3 for the manufacture of a pharmaceutical agent for the treatment of a condition which is mediated by beta-secretase.

6. The use according to claim 5 for the manufacture of a pharmaceutical agent for the treatment of Alzheimer's disease.

Abstract

The invention relates to novel beta-secretase inhibitors.

mh 04.06.2002